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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,297	02/17/2004	Apollon Papadimitriou	20619US1	9601

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,297	PAPADIMITRIOU, APOLLON	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/853,731.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of a modified sequence of human erythropoietin (EPO), $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ in the response filed October 20, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In the response to restriction requirement, applicants indicate the election of a specific modified sequence of human EPO is a species election, however, the office action dated October 20, 2004 (paragraph 1) indicates the election of one modified sequence is not a species election, rather an election of patentably distinct invention because each peptide with a specific sequence is considered patentably distinct. Therefore, claims 1-59 and the sequence modification of $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ are examined.

Informalities

The disclosure is objected to because of the following informalities:

2. Fig. 10 is objected to because the drawing and the label of Fig. 10 are on different pages. Appropriate correction is required.

Claim Objections

3. Claims 14, 17, 35 and 38 are objected to because the claims contain non-elected sequence modifications.

4. Claims 53, 55 and 57 are objected to because of the use of the term "$6.2^{\pm}0.2$". Use of "6.2 ± 0.2" is suggested.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 18, 22, 39 and 49-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 10/014,363. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 18, 22, 39 and 49-58 in the instant application disclose a liquid pharmaceutical composition comprising an EPO glycoprotein product having the in vivo biological activity, wherein the glycoprotein product is a pegylated EPO such as EPO being linked to $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$. This is an obvious variation in view of claims 1-16 in the copending application which disclose a conjugate comprising an EPO glycoprotein linked to $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$, and a pharmaceutical composition comprising the conjugate. Both the claims of the instant application and the claims of the copending application are directed to a pharmaceutical composition comprising a conjugate of EPO with poly(ethyleneglycol). Thus, claims 1, 18, 22, 39 and 49-58 in present application and claims 1-16 in the copending application are obvious variations of a pharmaceutical

composition comprising a conjugate of EPO with poly(ethyleneglycol) having the in vivo biological activity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-59 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 13-17, 19, 23-36, 38-42, 44, 48-55, 59-61, 67-77 and 83-89 of copending Application No. 09/853,731. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-59 in the instant application disclose a liquid pharmaceutical composition consisting essentially of an EPO glycoprotein product having the in vivo biological activity, a multiple charged inorganic anion and a buffer at pH of 5.5 to 7.0, and the liquid composition comprises a therapeutically effective amount of EPO product. This is an obvious variation in view of claims 1-11, 13-17, 19, 23-36, 38-42, 44, 48-55, 59-61, 67-77 and 83-89 in the copending application which disclose a liquid pharmaceutical composition comprising an EPO glycoprotein product having the in vivo biological activity, a multiple charged inorganic anion and a buffer at pH of 5.5 to 7.0, and the liquid composition comprises a therapeutically effective amount of EPO product and is stable at room temperature for at least 6 months and not containing urea.
Both the claims of the instant application and the claims of the copending application are directed to a pharmaceutical composition comprising an EPO glycoprotein product, a multiple charged inorganic anion and a buffer at pH of 5.5 to 7.0. Thus, claims 1-59 in present application and claims 1-11, 13-17, 19, 23-36, 38-42, 44, 48-55, 59-61, 67-77 and 83-89 in the copending application are obvious variations of a pharmaceutical

composition comprising an EPO glycoprotein product having the in vivo biological activity, a multiple charged inorganic anion and a buffer at pH of 5.5 to 7.0, and the liquid composition comprises a therapeutically effective amount of EPO product.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 4, 9, 25, 30 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 4 and 25 are indefinite because the claim cites citrate being a multiple charged inorganic anion, in fact citrate is an organic acid, not an inorganic anion.

9. Claims 9 and 30 are indefinite as to arginine/H_2SO_4/Na_2SO_4 being a buffer for pH 5.5-7.0 because arginine has a pKa of 1.8, 9 and 12.5, and H_2SO_4 is a strong acid, it is not clear how the combination can be used as a buffer.

10. Claim 58 is indefinite as to "poloxamers type 188 in an amount of 0.1 mg", it is not clear what concentration the poloxamers type 188 has since the volume of the solution is not indicated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-4, 6-9 and 11 are rejected under 35 U.S.C. 102(b) as anticipated by Yamazaki *et al.* (EP 0909564, April 25, 1997).

Yamazaki *et al.* disclose a solution preparation of EPO containing biologically active EPO including human EPO; an amino acid such as lysine, arginine or histidine as a stabilizer; polyethylene glycol; sugars; inorganic salt such as sodium chloride; and phosphate and/or citrate as a buffer with a pH of 5.0 to 8.0, and the solution containing therapeutically effective amount of EPO is administered to a patient by parenteral route (page 3; claims 1-4, 6-9 and 11).

12. Claims 1-4, 6, 7, 9-11, 22-25, 27, 28, 30-32 and 46 are rejected under 35 U.S.C. 102(b) as anticipated by Woog *et al.* (U. S. Patent 4,992,419).

Woog *et al.* disclose a compatible, storage-stable, aqueous or lyophilized EPO preparation containing human protein, phosphate or citrate buffer (20-100 mM), isotonic agent such as NaCl or mannitol at pH 6.5-7.4, and an amino acid such as arginine, and the preparation ensures the in-vivo effectiveness of the protein (column 1, lines 5-10; column 2, line 28-column 3, line 23; claims 1-4, 6, 7, 9-11), where phosphate is a multipli-charged inorganic anion and also a buffer. One preparation (Table 1, compositions a) contains 1000 U/ml of EPO, which corresponds to 10 or 5 μg/ml (the EPO preparation has an activity of 100,000 to 200,000 units/mg protein, corresponding to

100 to 200 units/μg; column 3, lines 25-30), 4 mg/ml NaCl (68 mM), 0.55 mg/ml of NaH_2PO_4 (5.3 mM), 5.0 mg/ml of Na_2HPO_4 (40 mM; claims 22-25, 27, 28, 30-32 and 46).

13. Claims 1-18, 22-39, 43, 46, 48-53, 55 and 59 under 35 U.S.C. 102(e) as being anticipated by Bailon (U.S. Patent No. 6,583,272, effective filing date, July 2, 1999).

The applied reference has a common assignee with the instant application. Based upon the earlier effective- U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1 .132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another" or by an appropriate showing under 37 CFR 1 .131.

Bailon teaches a conjugate comprising an erythropoietin (EPO) glycoprotein having at least one free amino group and having the in vivo biological activity and a poly(ethylene glycol) (peg) group; and a pharmaceutical composition comprising the conjugate and a pharmaceutically acceptable carrier (column 2, line 56-column 3, line 6; column 3, lines 41-47), wherein the EPO glycoprotein is selected from the group consisting of human EPO and analogs thereof which have sequence of human EPO such as SEQ ID NO:1 or 2 (claims 12, 33), modified by addition of 1 to 6 glycosylation sites or a rearrangement of at least one glycosylation site, e.g., the modification sequence $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ (column 5, line 28-column 6, line 5; claims 13-17, 34-39) and the glycoprotein is covalently linked to "n" peg groups of the formula $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$, where R is lower alkyl; x is 2 or 3; m is about 450-900; n is 1-3; and n and m are chosen such that the molecular weight of the conjugate minus the glycoprotein

is from 20 kDa to 100 kDa (column 2, line 56-column 3, line 6; column 3, line 48-column 4, line 4; Table 3; claims 18, 49-52). The peg-EPO is prepared in various formulations (Table 3; Example 8), e.g., formulation C containing 10 or 100 μg/ml peg-EPO, 10 mM (corresponding to 1.38 mg/ml) phosphate, 140 mM sodium sulfate, pH 6.2; formulation D containing 10 or 100 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate (corresponding to 5.68 mg/ml), pH 6.2; formulation E containing 50 or 400 μg/ml peg-EPO, 10 mM phosphate, 100 mM sodium chloride, pH 7.0; formulation G containing 400 μg/ml peg-EPO, 10 mM phosphate, 40 mM sodium sulfate, 3% mannitol (w/v), pH 6.2 (claims 1-11, 22-32, 43, 46, 48, 53, 55 and 59).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-4, 6-9, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamazaki *et al.* (EP 0909564) in view of Rosen *et al.* (WO 92/06116).

Yamazaki *et al.* disclose a solution preparation of EPO containing biologically active EPO including human EPO; an amino acid such as lysine, arginine or histidine as a stabilizer; polyethylene glycol; sugars; inorganic salt such as sodium chloride; and phosphate and/or citrate as a buffer with a pH of 5.0 to 8.0, and the solution containing therapeutically effective amount of EPO is administered to a patient by parenteral route (page 3; claims 1-4, 6-9 and 11). However, Yamazaki *et al.* do not disclose the amino

acid sequence of human EPO. Rosen *et al.* teach the amino acid sequence of recombinant human EPO (page 7, lines 32-34; SEQ ID NO:3 of WO 92/06116). At the time of invention was made, it would have been obvious that one of ordinary skill in the art is motivated to use the recombinant human EPO taught by Rosen *et al.* to prepare the pharmaceutical composition as taught by Yamazaki *et al.* (claim 12) because the use of recombinant protein would avoid the possibility of contamination from tissue. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

15. Claims 1-4, 6-9 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamazaki *et al.* (EP 0909564) in view of Rosen *et al.* (WO 92/06116) as applied to claims 1-4, 6-9, 11 and 12 above, further in view of in view of Elliot *et al.* (EP 0640619).

The combination of Yamazaki *et al.* and Rosen *et al.* disclose a solution preparation of EPO containing biologically active EPO including human EPO or erythropoietin having the amino acid sequence of SEQ ID NO:1 or 2; an amino acid such as lysine, arginine or histidine as a stabilizer; polyethylene glycol; sugars; inorganic salt such as sodium chloride; and phosphate and/or citrate as a buffer with a pH of 5.0 to 8.0 (page 3; claims 1-4, 6-9, 11 and 12). However, Yamazaki *et al.* and Rosen *et al.* do not disclose the use of a modified human EPO in the composition. Elliot *et al.* teach EPO analogs having at least one additional site for glycosylation or a rearrangement of at least one site for glycosylation, such as the modified EPO with $Asn^{30}Thr^{32}Val^{87}Asn^{88}Thr^{90}$ (page 3, lines 21-28; page 19, Table 3, line 22). At the time of invention was made, it would have been obvious that one of ordinary skill in the art is motivated to use the

modified human EPO taught by Elliot *et al.* to prepare the pharmaceutical composition as taught by Yamazaki *et al.* and Rosen *et al.* (claims 13-16) because the modified EPO having additional glycosylation site would have better in vivo activity due to its higher sialic acid content in the glycosylated protein. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

JON WEBER
SUPERVISORY PATENT EXAMINER

CMK
December 8, 2004